Reaction between 5-isopropylidene-2,2-dimethyl-1,3-dioxane-4,6-dione and trialkyl(aryl) phosphites in the presence of alcohols

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5-Isopropylidene-2,2-dimethyl-1,3-dioxane-4,6-dione (the condensation product of Meldrum's acid and acetone) reacts with trialkyl(aryl) phosphites in the presence of alcohols to produce dialkyl 2-[1-(dialkoxyphosphoryl)-1-methylethyl]malonate in good yields.

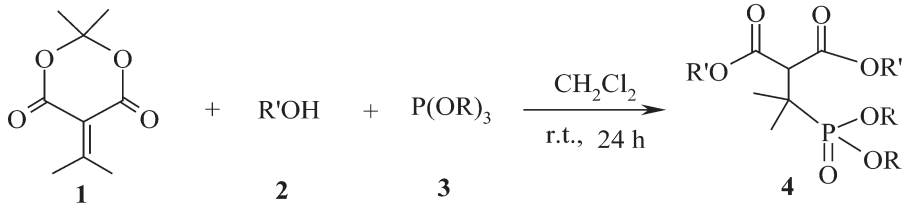
Keywords: Meldrum's acid, isopropylidene malonate, trialkyl(aryl) phosphites, alcohols

As versatile reagents and important intermediates, Meldrum's acid (isopropylidene malonate) and its derivatives have been widely used in organic synthesis.[1–3] The successful attack by nucleophilic trivalent phosphorus on a carbon atom is facilitated when the later is conjugated with a carbonyl group or when it is part of an unsaturated bond otherwise activated.[4–11] There have been many studies on the reactions between trivalent phosphorus nucleophiles and unsaturated carbonyl compounds in the presence of a proton source such as an alcohol.[3] The reaction of trimethyl phosphite and dimethyl acetylenedicarboxylate (DMAD) in the presence of alcohols is reported to produce phosphite ylide derivatives which are stable at low temperatures, but are converted to phosphonate derivatives by warming or by treatment with water.[12] There are some other recent reports on the reaction between phosphites and acetylenic esters in the presence of an acidic organic compound, all of which proceed to products through a phosphite ylide intermediate.[13–15] However, this intermediate has not been isolated or characterized in any of these reports as it is usually hydrolysed or rearranged to the corresponding phosphonates. In the context of our recent studies[16,17] on the reactivity of isopropylidene Meldrum's acid, we studied the reaction between 5-isopropylidene-2,2-dimethyl-1,3-dioxane-4,6-dione **1**, and trialkyl(aryl) phosphites **3** in the presence of an alcohol **2**. This reaction led to dialkyl 2-[1-(dialkoxyphosphoryl)-1-methylethyl]malonate **4** in good yields (Scheme 1). Here we report the results of our study on the reaction between isopropylidene Meldrum's acid and trialkyl(aryl) phosphites in the presence of alcohols.

Results and discussion

The reaction of isopropylidene Meldrum's acid **1** with trialkyl(aryl) phosphites **3** in the presence of alcohols **2** led to dialkyl 2-[1-(dialkoxyphosphoryl)-1-methyl-ethyl]malonates **4** in high yields (Scheme 1).

Compound **4a** was known and its structure was deduced by comparison of its spectral data with those of an authentic sample.[18] Compounds **4b–f** were new and their structures were deduced from their elemental analyses and spectral data. The mass spectrum of compound **4b** showed the molecular ion peak at *m/z* 282 whilst its ^{1}H NMR spectrum displayed two doublets (J_{HP} = 9.8 Hz) at 3.75 and 3.80 ppm for two $POCH_3$ groups and two singlets at 3.71 and 3.73 ppm for two methoxycarbonyl groups and a doublet for the methine proton at 3.67 ppm ($^3J_{HP}$ = 5.1 Hz). Two sharp signals were observed at 1.42 and 1.48 ppm attributed to the protons of two methyl groups. The ^{13}C NMR spectrum of compound **4b** showed ten



4	R	R'	Yield%*
a	Me	Et	88
b	Me	Me	90
c	Et	Me	92
d	Me	iso-Pr	92
e	Ph	t-Bu	87
f	Me	Bz	90

* Isolated yields

Scheme 1 Synthesis of dialkyl 2-[1-(dialkoxyphosphoryl)-1-methylethyl]malonate by reaction between isopropylidene Meldrum's acid and trialkyl(aryl) phosphites in the presence of alcohols.

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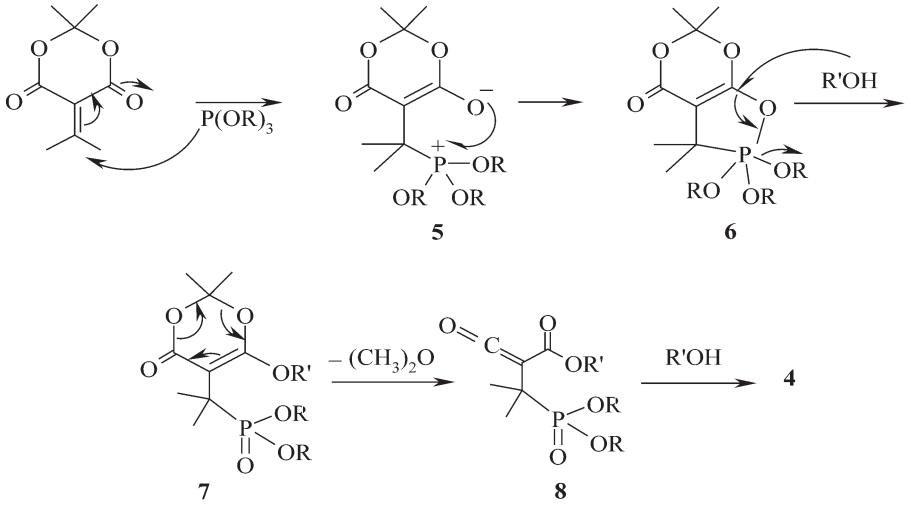

Scheme 2 Suggested mechanism for formation of compound **4**.

distinct resonances in agreement with the proposed structure. The structural assignments made on the basis of the NMR spectra of compound **4b** were supported by its IR spectrum, the ester carbonyl groups exhibited strong absorption bands at 1755 and 1742 cm^{-1}. The ^{31}P NMR spectrum of compound **4b** displayed a signal at 35.07 ppm. A reasonable mechanism for the formation of compound **4** is presented in Scheme 2. The initial addition of trialkyl(aryl) phosphite on isopropylidene Meldrum's acid leads to a diionic intermediate **5**. Cyclisation of this zwitterionic intermediate produces the oxaphosphorane **6**. The attack of the alcohol on **6** is initiated by conjugate addition to the double bond and cleavage of the phosphorus–oxygen bond by the nucleophile leads to an intermediate **7**, this intermediate first losses acetone to give ketene **8** and then the alcohol may attack **8** to produce **4**.

In summary, we report here that reaction between 5-isopropylidene-2,2-dimethyl-1,3-dioxane-4,6-dione and trialkyl(aryl) phosphites in the presence of alcohols provides a simple and efficient one pot route for the synthesis of dialkyl 2-[1-(dialkoxyphosphoryl)-1-methylethyl]malonate in excellent yields.

Experimental

Elemental analyses were performed using a Costech ECS 4010 CHNS-O analyser. Mass spectra were recorded on a FINNIGAN-MAT 8430 mass spectrometer operating at an ionisation potential of 70 eV. IR spectra were recorded on a Shimadzu IR-470 spectrometer. ^{1}H, ^{13}C and ^{31}P NMR spectra were recorded on Bruker DRX-300 Avance spectrometer in $CDCl_3$ using TMS as internal standard or 85% H_3PO_4 as external standard. The chemicals used in this work were purchased from Fluka (Buchs, Switzerland) and were used without further purification. Compound **1** was prepared as previously described in the literature.[19]

*Preparation of compounds (**4b–f**); general procedure*

To a magnetically stirred solution of isopropylidene Meldrum's acid (2 mmol) and an appropriate alcohol (4 mmol) in dichloromethane (15 mL) was added dropwise a mixture of trialkyl(aryl) phosphite (2 mmol) at room temperature over 2 min. The reaction mixture was then stirred for 24 h at room temperature. The solvent was removed under reduced pressure and the residue was purified by column chromatography on silica gel (60, 230–400 mesh) using ethyl acetate–hexane (3:1) mixture as eluent.

Dimethyl 2-[1-(dimethoxyphosphoryl)-1-methylethyl]malonate (**4b**): Yield: 90%; Yellow oil. IR (KBr) ν_{max}/cm^{-1}: 1755 and 1742 (C=O), Anal. Calcd for $C_{10}H_{19}O_7P$: C, 42.56; H, 6.79%. Found: C, 42.43; H, 6.91%. MS (*m/z*, %): 282 (M^+, 5). ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.42 and 1.48 (2s, 6H, $2CH_3$), 3.67 (1 H, d, $^{3}J_{HP}$ = 5.1 Hz, CH), 3.71 and 3.73 (6 H, 2 s, 2 OCH_3), 3.75 and 3.80 (6 H, d, $^{3}J_{PH}$ = 9.8 Hz, $2POCH_3$). ^{13}C NMR (75.47 MHz, $CDCl_3$): δ 20.17 and 20.23 (2 CH_3), 37.97 (d, $^{1}J_{cp}$= 143.9 Hz, P-*C*), 52.84 and 52. 86 (2 OCH_3), 53.45 and 53.97 (m, 2 $POCH_3$), 55.16 (d, $^{2}J_{CP}$ = 12.3 Hz, CH), 167.75 (d, $^{2}J_{CP}$ = 12.9 Hz, C=O), 171.15 (d, $^{3}J_{CP}$ = 20.3 Hz, C=O). ^{31}P NMR (121.5 MHz, $CDCl_3$): δ 35.07.

Dimethyl 2-[1-(diethoxyphosphoryl)-1-methylethyl]malonate (**4c**): Yield: 92%; Yellow oil. IR (KBr) ν_{max}/cm^{-1}: 1760 and 1735 (C=O), Anal. Calcd for $C_{12}H_{23}O_7P$: C, 46.45; H, 7.47%. Found: C, 46.63; H, 7.34%. MS (*m/z*, %): 310 (M^+, 7).^{1}H NMR (300 MHz, $CDCl_3$): δ 1.28 and 1.34 (6 H, 2 t, $^{3}J_{HH}$ = 7.3 Hz, 2 CH_3), 1.38 and 1.41 (6H, 2s, $2CH_3$), 3.67 (1 H, d, $^{3}J_{HP}$ = 5.1 Hz, CH), 3.69 and 3.86 (6 H, s, $2OCH_3$), 4.04–4.29 (4H, m, 2 OCH_2). ^{13}C NMR (75.47 MHz, $CDCl_3$): δ 15.83 and 16.02 (2 CH_3), 20.14 and 21.55 (2 CH_3), 34.09 (d, $^{1}J_{cp}$= 143.9 Hz, P-*C*), 52.98 and 53.16 (2 OCH_3), 55.33 (d, $^{2}J_{CP}$ = 12.3 Hz, CH), 66.55–67.50 (m, 2 $POCH_2$), 167.49 (d, $^{2}J_{CP}$ = 12.9 Hz, C=O), 171.32 (d, $^{3}J_{CP}$ = 20.3 Hz, C=O). ^{31}P NMR (121.5 MHz, $CDCl_3$): δ 35.10.

Di-iso-propyl 2-[1-(dimethoxyphosphoryl)-1-methylethyl]malonate (**4d**): Yield: 92%; Yellow oil. IR (KBr) ν_{max}/cm^{-1}: 1751 and 1729 (C=O), Anal. Calcd for $C_{14}H_{27}O_7P$: C, 49.70; H, 8.04%. Found: C, 49.79; H, 8.09%. MS (*m/z*, %): 338 (M^+, 5). ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.23 (12 H, d, $^{3}J_{HH}$ = 6.5 Hz, 2 $CHMe_2$), 1.35 and 1.40 (6H, 2s, $2CH_3$), 3.61 (1 H, d, $^{3}J_{HP}$ = 5.1 Hz, CH), 3.70 - 3.77 (6 H, m, $2POCH_3$), 5.01 (2H, sept, $^{3}J_{HH}$ = 6.5 Hz, 2 $CHMe_2$). ^{13}C NMR (75.47 MHz, $CDCl_3$): δ 20.14 and 21.67 (2 CH_3), 21.85 and 22.04 (2 $CHMe_2$), 35.26 (d, $^{1}J_{cp}$= 143.9 Hz, P-*C*), 57.22 (d, $^{2}J_{CP}$ = 12.3 Hz, CH), 61.53 and 62.89 (2 d, $^{2}J_{CP}$ 6.9 Hz, 2 $POCH_3$), 69.05 (2 $CHMe_2$), 167.73 (d, $^{2}J_{CP}$ = 12.9 Hz, C=O), 170.92 (d, $^{3}J_{CP}$ = 20.3 Hz, C=O). ^{31}P NMR (121.5 MHz, $CDCl_3$): δ 35.28.

Di-tert-butyl 2-[1-(diphenoxyphosphoryl)-1-methylethyl]malonate (**4e**): Yield: 87%; Yellow oil. IR (KBr) ν_{max}/cm^{-1}: 1756 and 1733 (C=O), Anal. Calcd for $C_{26}H_{35}O_7P$: C, 63.66; H, 7.19%. Found: C, 63.49; H, 7.28%. MS (*m/z*, %): 490 (M^+, 3). ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.42 and 2.51 (18 H, 2s, 2 CMe_3), 1.49 and 1.63 (6H, 2s, $2CH_3$), 3.57 (1 H, d, $^{3}J_{HP}$ = 5.1 Hz, CH), 7.16–7.55 (10 H, m, aromatic). ^{13}C NMR (75.47 MHz, $CDCl_3$): δ 20.37 and 21.80 (2 CH_3), 28.15 and 28.73 (2 CMe_3), 39.06 (d, $^{1}J_{CP}$ = 143.9 Hz, P-*C*), 58.02 (d, $^{2}J_{CP}$ = 12.3 Hz, CH), 83.41 ($OCMe_3$), 120.61 (d, $^{3}J_{CP}$ = 5.1 Hz, 4 CH_{ortho}), 126.79 (s, 2 CH_{para}), 130.07 (d, $^{4}J_{CP}$ = 7.8 Hz, 4 CH_{meta}), 149.94 (d, $^{2}J_{cp}$ = 10.3 Hz, C_{ipso}), 150.66 (d, $^{2}J_{cp}$ = 10.3 Hz, C_{ipso}), 167.90 (d, $^{2}J_{CP}$ = 12.9 Hz, C=O), 171.66 (d, $^{3}J_{CP}$ = 20.3 Hz, C=O). ^{31}P NMR (121.5 MHz, $CDCl_3$): δ 34.87.

Dibenzyl 2-[1-(dimethoxyphosphoryl)-1-methylethyl]malonate (**4f**): Yield: 90%; Yellow oil. IR (KBr) ν_{max}/cm^{-1}: 1753 and 1730 (C=O), Anal. Calcd for $C_{22}H_{27}O_7P$: C, 60.82; H, 6.26%. Found: C, 60.94; H, 6.14%. MS (*m/z*, %): 434 (M^+, 7). ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.30 and 1.44 (6H, 2s, $2CH_3$), 3.57 (1H, d, $^{3}J_{HP}$ = 5.1 Hz, CH), 3.78–3.89 (6H, m, $2POCH_3$), 5.11 (4H, s, 2 OCH_2), 7.28–7.58 (10 H, m, aromatic).^{13}C NMR (75.47 MHz, $CDCl_3$): δ 21.03 and 21.89 (2 CH_3), 36.06 (d, $^{1}J_{cp}$ = 143.9 Hz, P-*C*), 57.08 (d, $^{2}J_{CP}$ = 12.3 Hz, CH), 61.77 and 62.61 (2 d, $^{2}J_{CP}$ 6.9 Hz, 2 $POCH_3$), 66.75 (2 OCH_2), 128.03, 128.55, 128.71, 128.82, 129.03, 135.72 (aromatic), 168.35 (d, $^{2}J_{CP}$ = 12.9 Hz, C=O), 172.01 (d, $^{3}J_{CP}$ = 20.3 Hz, C=O). ^{31}P NMR (121.5 MHz, $CDCl_3$): δ 35.19.

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